

TOBACCO INDUSTRY RESEARCH COMMITTEE
350 FIFTH AVENUE NEW YORK 1, N. Y.

A. Budget Plan:

Salaries
Application For Research Grant

#120

Overhead (11%)
Other (Travel)

Date: December 6, 1955

1. Name of Investigator: 1. Leo G. Rigler, M.D.
2. Norman Zheutlin, M.D.
3. Borroughs Hill, Ph.D.
7. Anticipated Duration of: 4. Howard R. Bierman, M.D.

2. Title: 1. Director, Division of Postgraduate Medical Education & of Radiology. (Prof. of Radiology, University of Minnesota, on leave of absence) 2. Radiologist
3. Research Associate in Biochemistry of 4. Scientific Director; adequate
13. Institution and out-patient facilities:
& Address: City of Hope Medical Center
Duarte, California

4. Project or Subject: A Study of the Development of Carcinoma of the Lung in Smokers and Non-Smokers Subjected to the Influence of Smog.

9. Additional Requirements: 1. Assistant Radiologist (half time) \$6,750; 2. Physician \$8,500;
3. Radiology Technicians (2) \$8,000; 4. Radiology Technician \$4,500; 5. Experimental
Supplies, Glassware and chemicals \$2,500, x-ray film \$2,500, gas and oil \$500;
6. Equipment: fluoroscopic x-ray unit (1000) in a mobile van completely
equipped for radiography and laboratory work \$25,000 (first year only).

5. Detailed Plan of Procedure (Use reverse side if additional space is needed): The increased development of carcinoma of the lung in man is related to many factors, one of which has been alleged to be heavy cigarette smoking (1,2). Patients with carcinoma of the lung have, in large measure, been found to be exceptionally heavy smokers as compared with control groups (1,2). If cigarette smoking is truly a major causative factor in the development of carcinoma of the lung, it is surprising that a much higher incidence has not been found, strongly suggesting that other factors may be intimately involved (3). The relatively high rates of carcinoma of the lung in urban areas as compared to rural areas demands a thorough scrutiny of air pollution by smog and possibility of the activity of toxic acid components and irritants. It may be possible to detect subclinical cases in their early pathological state. It would appear necessary, therefore, to determine the influence of a combination of environmental and host factors such as: cigarette smoking, air pollution (smog), heredity, occupation, etc. upon the development of pathoses in the lung (3). Summary of this project was reported in Cancer 62, May 1953.

It is proposed to study carefully 10,000 male subjects, 45 years of age or older, for a period of at least five years. A group will be selected with strong hereditary cancer histories and other similar attributes which would favor an increased incidence of carcinoma of the lung. The incidence of carcinoma of the lung in 4,000 heavy smokers (two packs or more a day) from the smog areas would be compared with a control group of 4,000 heavy smokers in smog-free areas, 10,000 non-smokers in heavy smog areas and 1,000 non-smokers living in the surrounding environs of Los Angeles out of the smog area. The subjects will be selected from the aircraft manufacturing and other industries where the population is stable, willing to cooperate, and available for study by a mobile x-ray and laboratory unit.

Air pollution in the form of smog has been shown to have carcinogenic properties (4a) and the possibility of a co-carcinogenic action between smoking and smog in man (4b) is a

a/ Nori Brandler

Business Officer of the Institution

Assistant to Executive Vice President and
Financial Officer

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6. Budget Plan:

Salaries (Inc. 2% Soc. Sec.)	\$27,489
Expendable Supplies	9,800
Permanent Equipment	29,000
Overhead (15%)	9,943
Other (travel)	500
Total	\$76,732

Date December 6, 1955

1. Name of Investigator: 1. Leo G. Rigler, M.D.
2. Norman Zheutlin, M.D.
3. Harrold Hill, Ph.D.
7. Anticipated Duration of Work: 5 years minimum

2. Title: Director, Division of Postgraduate Medical Education & of Radiology. (Prof. of Radiology, University of Minnesota, on leave of absence)
3. City of Hope Medical Center Division of Research, 27 full time people; adequate laboratories and out-patient facilities.
4. Address: City of Hope Medical Center, Duarte, California

4. Project or Subject: A Study of the Development of Carcinoma of the Lung in Smokers and Non-Smokers Exposed to the Influence of Drug.

9. Additional Requirements: 1. Assistant Radiologist (half time) \$6,250; 2. Physician \$8,500; 3. Biochemistry Technicians (2) \$8,000; 4. Radiological Technician \$4,200; 5. Expendable Supplies: Glassware and chemicals \$2,300, x-ray film \$7,000, gas and oil \$500; 6. Permanent equipment: Photofluorographic x-ray unit (4x5) in a mobile van completely equipped for radiography and laboratory work \$29,000 (first year only)

5. Detailed Plan of Procedure (Use reverse side if additional space is needed. The investigator may request an oral report.)
10. Additional Information (Including relation of work to other projects and other sources of supply):
be heavy cigarette smoking (1,2). Patients with carcinoma of the lung. In 1952, an incidence of cancer in 460 per. out of a group of 188,079 persons interviewed in 1952, an incidence of cancer in 460 per. If 100,000 has been uncovered in heavy smokers. Thus it can reasonably be expected that there is a highly selected population of 4,000 heavy smokers (male) that at least 10 to 20 patients with carcinoma of the lung should become detectable by average clinical standards in the course of a two year period. By prescreening carefully in this group in addition to the predictability of the activity of lactic acid dehydrogenase and isomerase it may be possible to detect additional cases in their early subclinical state. It would appear necessary, therefore, to determine the influence of a combination of environment (This proposed research would be similar to the "Pulmonary Neoplasm Research Project", a preliminary report of which appeared in J.A.M.A. 157:440-444, Jan. 29, 1955. A summary of this project also appeared in Ca5:3-82, May 1955)
It is proposed to study carefully 10,000 male subjects, 45 years of age or older, for a period of at least five years. A group will be selected with strong hereditary cancer histories and other similar attributes which would favor an increased incidence of carcinoma of the lung. The incidence of carcinoma of the lung in 4,000 heavy smokers (two packs or more a day) living in the same area would be compared with a control group of 4,000 heavy smokers in non-lung areas, 10,000 non-smokers in heavy smoke areas and 1,000 non-smokers living in the surrounding environs of the lung areas out of the smoke areas. The subjects will be selected from the aircraft manufacturing and other industries in the area. The subjects will be selected to cooperate, and available for study by the Director of Project Laboratory Unit.

air pollution in the form of smog has been shown to have carcinogenic properties (4a) and the possibility of a co-carcinogenic action between smoking and smog in man (4b) is a

s/ Mort Brandler

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5. (continued)

vital question that needs a direct approach. The incidence of carcinoma of the lung in the Los Angeles County General Hospital has been carefully recorded by Steiner (5) and may be employed for comparative purposes. It would appear that the Los Angeles County area is ideal for such a study because of its large variegated population, the prevalence of smog, and the sympathetic interest of the inhabitants toward the problem. The City of Hope Medical Center is located 20 miles from the center of Los Angeles, equidistant from areas free of or heavily saturated with smog. The status of air pollution is available from the Air Pollution Control District.

Patients will be restudied at 4 to 6 month intervals. The plants will be visited by a mobile unit to take films and blood. Postero-anterior and lateral chest roentgenograms will be taken on these subjects on 4 x 5 cut film by photofluorography. Comparison studies will be made with a view to detecting minimal changes suggesting abnormality. Re-examination with life size (14 x 17) films will be done on all cases showing abnormality. This would require approximately 60,000 minifilms and approximately 3,000 14 x 17 films per year. Intensive histories including hereditary, family, and social backgrounds will be obtained on all patients by a combined questionnaire and personal interview technic developed and employed at City of Hope Medical Center (6). Careful records of weight, smoking habits, etc. will be maintained.

The lactic acid dehydrogenase (LDH) activity of the serum of all patients will be determined on every other visit (7,8,9). The micro-technic permits the determination on finger tip blood. The lactic dehydrogenase activity has been found to be elevated in the sera of many patients with cancer and leukemia, but has not been raised consistently in other diseases. Significant elevations have been found in a number of very early cases of cancer and leukemia. This study of a selected group of individuals among whom the incidence of lung cancer may be expected to be increased over the average population over a five year period could afford valuable data in establishing the possible predictive value of this enzyme determination in cancer detection.

The LDH technic was devised by Dr. Borroughs Hill, Research Associate in the Department of Biochemistry, and the laboratory and equipment for this determination are available.

The hexosephosphate isomerase level in the blood has been reported by Bodansky et al. to be elevated early in neoplastic diseases (10). Determination of the isomerase level will be done on all patients every other visit (each eight months). Some estimation of its value will also thus become available.

All patients in whom suspicious findings of pulmonary neoplasm were revealed would be studied more carefully for changes in pulmonary function employing the mass spectrometer technics developed by Tokuyasu, Coblentz, and Bierman (11), Papanicolaou's smears, bronchograms, planigrams, etc. in collaboration with the patient's physician.

Dr. Leo C. Rigler and Dr. Norman Zheutlin will supervise and assist in interpretation of films in an effort to detect the early development of carcinoma of the lung. Dr. Rigler has had extensive experience in film screening for large Public Health Service projects (12,13,14).

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